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Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

See the attached.

1 - PATENT APPLICATION FILE COPY

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BEFORE THE BOARD OF PATENT APPEALS

AND INTERFERENCES

Paper No. 41

Application Number: 08/249689

Filing Date: 5/26/94

Appellant(s): Paul R. Schimmel

Patrea L. Pabst

For Appellant

EXAMINER'S ANSWER

This is in response to Appellant's brief on appeal filed 10/21/96.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The Appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is deficient because summary does not state that the invention is drawn to a compound that specifically inhibits a targeted ribonucleic acid molecule, or that the critical site identified by the method must comprise a minor groove.

The invention is drawn to a method of designing a compound specifically inhibiting the function of a targeted ribonucleic acid molecule comprising the steps of:

(a) determining the sequence of a site in the targeted ribonucleic acid molecule that is critical to function of the targeted ribonucleic acid molecule;

(b) determining the secondary and tertiary structure of the targeted ribonucleic acid molecule, including the position of the critical site relative to the major and minor grooves;

(c) designing and synthesizing a compound that inhibits the function of the targeted ribonucleic acid molecule by binding specifically to the minor groove of the critical site.

The claimed compounds are made by the claimed method.

(6) Issues

The Appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The Appellant submits that the claims stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

Yamada, T. et al. "The translocation inhibitor tuberactinomycin binds to nucleic acids and blocks the in vitro assembly of 50S subunits." Nucleic Acids Research, vol. 8, no. 23 (1980), pp. 5767-5777.

Rebek, J. Jr. et al. "Molecular recognition: Hydrogen bonding and stacking interactions stabilize a model for nucleic acid structure." J. Am. Chem. Soc., vol. 109, (1987) pp. 5033-5035.

Jeong, K. et al. "Molecular recognition: Hydrogen bonding and aromatic stacking converge to bind cytosine derivatives." J. Am. Chem. Soc., vol. 110, (1988), pp. 3327-3328.

Askew, B. et al., "Molecular recognition with convergent functional groups. Synthetic and structural studies with a model receptor for nucleic acid components." J. Am. Chem. Soc., vol. 111, (1989), pp. 1082-1090.

Wilson, W. et al., "The search for structure-specific nucleic acid-interactive drugs: Effects of compound structure on RNA versus DNA interaction strength." Biochemistry, vol. 32, (1993), pp. 4098-4104.

(10) New Prior Art

A new reference has been applied in a new ground of rejection in this examiner's answer and is(are) listed below:

Michel, F. et al., "Visualizing the logic behind RNA self-assembly.", Science, vol. 273, (1996), pp. 1676-1677.

(11) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

Claims 1 and 3-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to practice the claimed invention one of skill in the art must determine a site critical for the function of a targeted functional RNA molecule that comprises a minor groove such that when a compound specifically binds to the minor groove of the critical site, the function of the RNA molecule is inhibited. It is not predictable that such critical sites exist in all RNA molecules. The method requires that one must determine the secondary and tertiary structure of the targeted RNA molecule. It is not predictable that the secondary and tertiary structures of all RNA molecules could be determined by a skilled practitioner at the time of

filing of the instant application because the determination of tertiary structure requires growth of a crystal of the RNA molecule that is suitable for X ray crystallography and growth of such crystals is unpredictable. One must further design and synthesize a compound that binds specifically to the critical site in the minor groove of the targeted RNA molecule and thereby inhibit the function of the targeted RNA molecule. It is not predictable that such a compound could be designed and synthesized by a skilled practitioner at the time of filing of the instant application. Because of the unpredictability of practicing all steps of the claimed invention, at least a large amount of experimentation would be required to practice the claimed invention.

b) The specification provides general guidance on pages 9-37 to mutate and assay tRNA molecules to determine sites of mutations that inhibit aminoacylation. The specification provides general guidance on pages 37-38 to use known computer modeling programs to test hypothetical structures of molecules for interaction with a substrate of known structure. The specification provides general guidance on pages 38-39 to use the methods known by one of skill in the art to synthesize peptides or other organic compounds. The specification does not provide guidance to isolate mutations in a minor groove of RNA that inhibit the function of RNA molecules other than tRNA. The specification does not provide guidance for determining the secondary and tertiary structure of RNA molecules other than tRNA. On page 36, lines 22-24. the specification states, "The interpretation of experiments on systems other than tRNAs, such as M1 RNA of RNase P, are hampered by the lack of three dimensional structural information". The specification does not provide specific guidance for designing a

compound using computer modeling programs that specifically interacts with a critical site comprising a minor groove on an RNA molecule. On page 38, lines 7-8, the specification states "computer modeling has not been used to design compounds that will bind to and inactivate RNA". On page 38, lines 7-8, the specification states "computer modeling has not been used to design compounds that will bind to and inactivate RNA". The specification does not provide specific guidance for making the claimed pharmaceutical compositions of claims 9, 10, or 13.

c) The specification does not provide a working example of a site critical for the function of a targeted functional RNA molecule that comprises a minor groove such that when a compound specifically binds to the minor groove of the critical site, the function of the RNA molecule is inhibited. The specification does not provide a working example of the secondary and tertiary structure of an RNA molecule other than a tRNA molecule. The specification does not provide a working example of using computer modeling programs to design a compound that specifically interacts with a critical site comprising a minor groove on an RNA molecule resulting in inhibition of the function of the RNA molecule. The specification does not provide a working example of designing a compound that specifically interacts with a critical site comprising a minor groove on an RNA molecule resulting in the inhibition of the function of the RNA molecule. The specification does not provide a working example of making the claimed pharmaceutical compositions of claims 9, 10, or 13.

d) The invention is drawn to a method of designing a compound that specifically interacts with a minor groove of a critical site on an RNA molecule resulting in inhibition of the function of the RNA molecule and the compounds produced by the method.

e) The prior art shows the secondary and tertiary structure of tRNA molecules. The prior art does not show the secondary and tertiary structure of mRNA, rRNA, or other RNA molecules larger than tRNA, as shown on page 36, lines 22-24. Michel et al. show on page 1676 that it was not until 1996 that the crystal structure of an RNA molecule larger than tRNA was solved. The prior art does not show computer-aided design of compounds that bind to and inactivate RNA as shown in the specification on page 38, lines 7-8. The prior art does not show compounds that specifically interact with the minor groove of RNA molecules and thereby inhibit the function the RNA molecule. The prior art does not show the pharmaceutical use of compounds that inhibit the function of an RNA molecule by binding to the minor groove of a critical site. Tuberactinomycin is a potent antibiotic that Yamada et al. shows binds to RNA and can inhibit protein translation and splicing of group I introns. Tuberactinomycin binds to individual nucleotides in RNA molecules but has not been shown to bind to the minor groove of an RNA molecule. The references cited by the applicant on page 43 of the specification as dealing with small molecules that bind to nucleic acids (Rebek et al., 1987; Jeong et al., 1988; and Askew et al., 1989) discuss the interaction of synthetic molecules with purines and pyrimidines rather than nucleic acids. Wilson, et al., published three years

after the effective priority date of the parent application, summarize the field of designing molecules that bind RNA as follows:

> It is interesting that no classes of small molecules have been defined that bind strongly in the minor groove of RNA or in the major groove of either RNA or DNA. The question of what types of small molecules bind in the grooves of RNA is extremely important for the design of RNA interactive drugs. There are no outstanding paradigms at this point to suggest design directions for RNA groove-binding drugs.

f) The skill of those in the art of nucleic acid structure is high.

g) It is not predictable that the secondary and tertiary structure of any RNA molecule can be determined, as discussed above. It is not predictable which nucleotides are critical for function of an RNA molecule. For example, the specification teaches the unpredictability of the effect of introducing an amber anticodon into a tRNA molecule on Page 15. The unpredictability of mutated amber suppressor tRNAs when used in the "transplantation assay" is discussed on Pages 15-17. It is unpredictable whether a site that when mutated inhibits the function of an RNA molecule will lead to the identification of the claimed critical site with a functional wild type sequence that comprises a minor groove, such that when a compound specifically binds to the minor groove of the critical site, the function of the RNA molecule is inhibited. In some cases a critical site identified by a loss-of-function mutation will be located in a single stranded region that does not comprise the major and minor grooves present in double-stranded nucleic acid, as pointed to in the specification on page 31, lines 3-5 and page 36, lines 4-10. In cases in which a critical site identified by a loss-of-function mutation is in a region comprising a minor groove, it is unpredictable whether the secondary and tertiary

structure of the RNA molecule will permit a compound to bind to the critical site, or whether binding of the compound will result in inhibition of function of the RNA molecule. It is further pointed out that it is unpredictable whether binding of a compound to an RNA molecule will inhibit the function of the RNA molecule because the inhibition of function of an RNA molecule requires that the compound both bind to the RNA molecule and inhibit a functional interaction between the RNA molecule and its normal cellular substrate, such as a ribosome or a transcription complex It is unpredictable whether computer-aided design can be used to design a compound that specifically interacts with a minor groove of a critical site in an RNA molecule resulting in the inhibition of the function of the RNA molecule, because the specification provides no specific guidance or working examples of computer-aided design of such a molecule and states on page 38. lines 7-8 that design of a compound that will bind to and inactivate RNA has not been shown in the prior art. It is unpredictable whether the claimed pharmaceutical compositions can be used for a therapeutic purpose because it is not predictable, as discussed above, whether the claimed compounds can be made, and further because it is unpredictable whether the compounds, if made, will have sufficient stability, safety, and effectiveness for use as a pharmaceutical composition.

h) The claims are broadly drawn because the claims encompass a multitude of RNA target molecules, and it is unpredictable whether the claimed method can be practiced in any embodiment, and it is unpredictable whether any embodiment of the claimed compounds can

be designed, and it is unpredictable whether the claimed pharmaceuticals can be made and used.

The skilled practitioner would have first turned to the specification for guidance in practicing the claimed invention. However, as set forth above, the specification does not provide specific guidance or working examples of the claimed method or products. As such, the skilled practitioner would next have turned to the prior art for such guidance. However, as set forth above, the prior art does not show the claimed methods or products and does not provide the necessary guidance for practice of the claimed invention. Wilson et al. teaches that the claimed methods and products were still unknown three years after the effective priority date of the instant application. Finally, said practitioner would have been forced to turn to trial and error experimentation in an art which, as evidenced above, was unpredictable based on the disclosure of the instant application or knowledge derived from the prior art. Such represents undue experimentation.

(12) New Ground of Rejection

This examiner's answer contains the following NEW GROUND OF REJECTION.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 11, 12, and 17-19 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 15-19 of copending Application No. 07/929834. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

This examiner's answer contains the following NEW GROUND OF REJECTION.

Double Patenting

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting

ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-6, 8-10, 13-16, 20, and 21 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 8-10, 12-14, and 22 of copending Application No. 07/929834. Although the conflicting claims are not identical, they are not patentably distinct from each other because the differences between the instant claims and the cited claims of Serial No. 07/929834 are minor in nature.

Claim 1 of the instant application is drawn to a method of designing a compound that specifically inhibits a targeted RNA molecule by interacting in a minor groove of a critical site, the method including a step of synthesizing the claimed compound. Claim 3 is drawn to the method of claim 1 further limited to a target RNA molecule selected from the group consisting of mRNA, rRNA, tRNA, and viral RNA. Claim 4 is drawn to the method of claim 1 further limited to a compound that inhibits protein synthesis. Claim 5 is drawn to the method of claim 4 further limited to protein synthesis inhibited in a cell selected from a group consisting of tumor cells, virally infected cells, and bacterial cells. Claim 6 is drawn to the method of claim 1 further limited to a design of the compound that involves calculation of minimum energies of

interaction with the target RNA molecule. Claim 8 is drawn to the method of claim 1 further limited to a target RNA molecule that is a tRNA, and determination of the critical site by a process of mutational analysis. Claim 9 is drawn to the method of claim 1 further limited to determining an effective amount of the compound and combining the compound with a pharmaceutical carrier. Claim 10 is drawn to the method of claim 9 further limited to a pharmaceutical carrier that is suitable for topical, parenteral, or enteral administration. Claim 13 is drawn to compound of claim 11 further limited to comprising a pharmaceutical carrier suitable for topical, parenteral, or enteral administration. Claim 14 is drawn to the method of claim 3 further limited to a critical site in the minor groove of an acceptor stem of a tRNA molecule. Claim 15 is drawn to the method of claim 14 further limited to a tRNA molecule that is $tRNA^{Ala}$. Claim 16 is drawn to the method of claim 15 further limited to a critical site that is the G3:U70 base pair. Claim 20 is drawn to the method of claim 1 further limited to a compound that is synthesized from a retroviral vector. Claim 21 is drawn to the compound of claim 11 further limited to a compound synthesized from a retroviral vector.

Claim 1 of co-pending application Serial No. 07/929834 differs from claim 1 of the instant application by concluding with a step drawn to designing a compound. Co-pending claim 14 differs from instant claims 10 and 20 by listing a group of pharmaceutical carriers that includes a retroviral vector. Co-pending claim 22 differs from instant claims 13 and 21 by listing a group of pharmaceutical carriers that includes a retroviral vector.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of claim 1 of co-pending Serial No. 07/929834 by including a step of synthesizing the designed molecule because the synthesized molecule could be used for the purpose of inhibiting the activity of the target RNA molecule. Regarding the retroviral vector of instant claims 20, and 21, it would have been further obvious to select a pharmaceutical carrier consisting of a retroviral vector because such a retroviral vector is listed in the group of acceptable pharmaceutical carriers in claims 14 and 22 of co-pending application Serial No. 07/929834.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

(13) Response to argument

Appellant's arguments filed 10/21/96 have been fully considered but they are not persuasive.

The Appellants state on page 8 of their Appeal Brief filed 10/21/96 that it is appropriate to provide the bulk of the guidance for practicing the invention through reference to prior art procedures. This is agreed with, as stated in the Advisory Action mailed 7/30/96. The amount of guidance or direction needed to enable the inventions inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. The more that is known in the prior art about the nature of the invention, how to make, and how to use the

invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. Because the prior art does not show the steps of the method of the claimed invention or the claimed products, and it is unpredictable whether critical sites of the claimed invention can be determined and it is further unpredictable whether compounds can be designed that bind to the minor groove of a targeted RNA molecule resulting in the inhibition of function of the targeted RNA molecule, there is a greater burden required for the specification to provide guidance to make and use the claimed invention. It is agreed that the specification provides guidance for determining loss-of -function mutations in tRNA molecules. However, the claimed invention is not drawn to loss-of-function mutations, rather it is drawn to a method of determining critical sites on functional RNA molecules that comprise a minor groove and the design of compounds that bind to the minor groove of the identified critical site resulting in the inhibition of the wild type RNA molecule. For the reasons discussed in the Grounds of Rejection section above, identification of a loss-of -function mutation is only a possible first step toward identifying the claimed critical site in a functional RNA target molecule. Subsequent steps required for the identification of the claimed critical site are unpredictable for the reasons discussed above. The Appellants state that on page 9 of their Appeal Brief filed 10/21/96 that procedures for determination of the tertiary structure of RNA molecules were well known at the time of filing. However, Michel

et al. establish that it was not until 1996 that structures of RNA molecules larger than tRNA were known. The Appellants state on page 9 of the Appeal Brief that the specification shows examples of molecules which interact with specific RNA sequence structures. However, the cited passage discloses interactions of proteins and DNA, and further discusses interaction of tRNA with tRNA synthetases. It is noted that the interaction of tRNA and tRNA synthetases does not result in an inhibition of function of the tRNA. The Appellants state on page 9 of the Appeal Brief that the specification shows on pages 37-39 procedures for modeling and synthesis of compounds. However, the guidance is of a general nature that does not provide specific guidance to make the claimed compounds. On pages 9-10 of the Appeal Brief the Appellants state that the claims are not directed towards a therapeutic compound. However, claims 10 and 13 are drawn to a method of making a pharmaceutical composition and a pharmaceutical composition, respectively, that comprise the claimed RNA inhibiting molecule. Weight is given to the claim of a pharmaceutical composition such that the specification must enable pharmaceutical use of the claimed composition. On pages 12-13 of the Appeal Brief, the Appellants state that all steps of the claimed invention are enabled and that absence of a single complete working example should not be used to question enablement. However, as discussed above, because the specification and the prior art fail to show any of the steps of the claimed invention, the lack of a working example is a proper factor to consider in deciding whether undue experimentation is required to make and use the claimed invention. The Appellants state on page 8, lines 2-4, that "each of the steps of the claimed method represent

determinations which have been performed, in isolation or in partial combination, on numerous RNA molecules", but the Appellant does not point to examples in the specification or the prior art of steps (c) and (d) of claim 1 for molecules other than tRNA, or step (e) of claim 1 for any targeted RNA molecule. The Appellants state on page 14 of the Appeal Brief that the specification shows on pages 37-38 and 18-22 examples of inhibitory compounds, but the passages do not describe the claimed compounds that interact with the minor groove of RNA. The Appellants contest the relevance of Wilson et al. Wilson et al. was cited to show that the prior art (as summarized in Wilson et al.) did not show the claimed invention, and that enablement beyond that shown in the prior art is required to practice the claimed invention. The Appellants state on page 18 of the Appeal Brief that the Askew et al. reference shows interaction of compounds with nucleic acids. Askew et al. does not show interactions of compounds with functional RNA molecules. On page 1087, Askew et al. concludes by saying "It should be possible to develop agents capable of specific recognition of single-stranded nucleic acids involving a tRNA, is shown in Scheme II. We are progressing toward these goals". This passage suggests that compounds that specifically interact with adenines of RNA were not yet available. It is further pointed out that Askew et al. do not show compounds binding to the minor groove of RNA, as in the claimed invention, or compounds that inhibit the function of an RNA molecule. The Appellants state on page 18 of the Appeal Brief that Rebek et al. discusses compounds which can be used to bind to the major and minor grooves of nucleic acids. Rebek et al. does not show interaction of compounds with RNA, or the minor

groove of RNA. The Appellant's state that the Declaration filed under 37 C.F.R 1.132 on 7/30/92 shows that one of skill in the art could routinely design the claimed compounds. However, it is evident from the state of the prior art that the design of such compounds was not routine because the claimed compounds had not been made 3 years after the effective filing date of the instant application.

(14) Period of Response to New Ground of Rejection

In view of the new ground of rejection, Appellant is given a period of TWO MONTHS from the mailing date of this examiner's answer within which to file a reply to such new ground of rejection. The reply may include any amendment or material appropriate to the new ground of rejection. Prosecution otherwise remains closed. Failure to respond to the new ground of rejection will result in dismissal of the appeal of the claims so rejected.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

jsb 1/17/96

Assistant Commissioner for Patents
Washington, D.C. 20231